SUPPORT FOR THE AMENDMENTS

Claims 1, 13, and 19-21 were previously canceled.

Claims 4 and 24 are presently canceled.

Claims 14 and 16 have been amended.

Claims 36 and 37 have been added.

Support for the amendment of Claims 14 and 16 and for the introduction of Claims 36 and 37 is supported by original Claims 1-21.

No new matter has been entered by the present amendments.

REMARKS

Claims 2-12, 14-18, and 22-35 are pending in the present application.

The rejection of Claims 9-11 under 35 U.S.C. §112, first paragraph (written description), is respectfully traversed.

Applicants agree that "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). However, in the case at hand the disclosure of the oxygen absorbers in Claims 9-11 in the specification is sufficient to satisfy this requirement.

In the Office Action, the Examiner again relies upon a string of case citations including *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, (Fed. Cir. 1991), *Univ. of Rochester v. G.D. Searle*, 69 USPQed 1886, 1892 (Fed. Cir. 2004), *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993), *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993), *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997), and *In re Gostelli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). As previously asserted, although these cases are fine cases, the current cut-and-paste exercise from the MPEP fails to address the real issue at hand.

The real issue with respect to whether a written description exists is whether the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) In the case at hand, Applicants

submit that the skilled artisan would readily appreciate the full scope of oxygen absorbers and that the present inventors were in possession of the same, even oxygen absorber selected from the group consisting of a humidity-activated oxygen absorber, a self-activating absorber, an ultraviolet-radiation-activated absorber, a radiation-activated absorber, a microwaves-activated absorber, an absorber activated by a combination of activation processes, or an absorber without necessity of activation.

At page 3, lines 8-32, Applicants state the following:

> In addition to the above-mentioned methods, a new method for the preservation of substances susceptible to oxidation with the use of substances trapping air oxygen, often called oxygen absorbers, has been developed. Mitsubishi Gas Chemical (Tokyo, Japan) have developed bags absorbing oxygen based on a reaction of iron under the trade name Ageless (Yoshikawa, Y., Amemiya, A.; Komatsu, T.; Inoue, Y.; Yuyama, M., Oxygen Absorbent for Food Packaging. Jpn. Kokai Tokkyo Koho, Showa 56-33980, 1978). Similar products are also offered, for example, by Multisorb Technologies, Inc. under the trade name Fresh Pax™ or by Standa Industry under the trade name ATCO.
>
> Many products are available nowadays. They are based on humidity-activated oxygen absorbers, self-activating absorbers, ultraviolet-radiation-activated absorbers, radiation-activated absorbers, microwaves-activated absorbers, absorbers activated by a combination of activation processes, or absorbers not requiring any activation.
>
> In patent application US 2002/0132359, the use of these absorbers for pharmaceutical preparations sensitive to oxygen is applied for protection. The application is carried out in a blister packing where the absorber is situated between the lid and the blister itself. The application further informs that it is very difficult to find out which of the substances will be susceptible to oxidation. The problem subsists in the fact that often the oxidation does not follow the classical Arrhenius equation, and that is why accelerated stability tests, which are successfully used for other decomposition reactions, fail. The patent application further contains a list of some pharmaceutical substances, which could be sensitive to oxygen. HMG–CoA inhibitors simvastatin or lovastatin are the most relevant ones among them. Both these substances contain a system of conjugated double bonds in a carbocyclic system, which can result in sensitivity to oxygen.

Thus, the scope of oxygen absorbers was well-known to the skilled artisan as of the date of the present invention, even oxygen absorber selected from the group consisting of a humidity-

activated oxygen absorber, a self-activating absorber, an ultraviolet-radiation-activated absorber, a radiation-activated absorber, a microwaves-activated absorber, an absorber activated by a combination of activation processes, or an absorber without necessity of activation. To this end, it has been well-established that "The description need only describe in detail that which is new or not conventional". See *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); *Fonar Corp. v. General Electric Co.*, 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997).

Further, "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.").

Thus, the issue in the present case, when properly framed, is whether the artisan would have appreciated Applicants to be in possession of the full scope of the claimed invention and whether they would recognize that scope. Clearly, based on page 3 of the specification, this is the case as the oxygen absorbers are convention and well-known to the skilled artisan. Moreover, it must be kept in mind that "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

Despite the foregoing, the Examiner alleges that Waterman (US 2002/0132359) teaches two specific types of oxygen absorbers - a humidity-activated oxygen absorber and an

ultraviolet-radiation-activated absorber. The Examiner is incorrect, however, in the assertion that Waterman fails to establish that the other oxygen absorbers are conventional. Indeed, reference is made, at least, to paragraphs [0030] – [0031] of Waterman, which states:

> [0030] If a water-initiated oxygen-absorber is used, then a sufficient amount of moisture to initiate the oxidation process is introduced prior to sealing the lid to the blister. This may be achieved by controlled water addition (humidity exposure) before or during packaging. Suitable *water-initiated, oxygen-absorbers* include metal-based absorbers such as particulate-type iron (e.g., hydrogen reduced iron, electrolytically reduced iron, atomized iron, and milled pulverized iron powders), copper powder, and zinc powder. A preferred metal-based absorber is an iron powder. A moisture-holding material may be incorporated with the absorber to provide a *self-activated system*. Suitable moisture-holding materials include activated carbon, silicas, zeolites, molecular sieves, hydrogels, and diatomaceous earth. The particular moisture-holding materials used will depend upon the humidity level of the environment. For example, in a very low humidity environment, a moisture carrying material such as a hydrogel that partially binds water may be preferred rather than a simple moisture absorbent (or desiccant). An accelerator may also be incorporated such as a metallic iodide or bromide as described in U.S. Pat. No. 6,133,361, incorporated herein by reference. An example of a suitable thermoplastic resin containing an oxygen absorber is Amosorb.TM. 3000 (available from BP Amoco Chemicals). Other resins appropriate for the current invention include those made using ascorbic acid or other easily oxidized organic compounds.
>
> [0031] A preferred oxygen absorbing material is an *absorber activated by ultraviolet-light*. The UV-photo-activated absorber may be activated by exposing the absorber to UV light immediately before insertion of the dosages into the packaging, or in some cases, by exposure to UV light through the blister itself after sealing with the drug. This last approach assumes that the blister is sufficiently transparent to the UV light to allow activation of the absorber and the drug is stable to the light exposure. Suitable *UV-activated oxygen absorbers are described in US Patent Nos. 6,139,770 and 6,057,013*, incorporated herein by reference. It will be appreciated by those skilled in the art that the oxygen absorbing material may be compounded with other materials (such as polymers and plasticizers) in order to render the resulting blend co-extrudable with the other materials as part of the construction. For optimization, properties such as extrudability, adhesion and thermoformability are generally considered. The amount of absorbing resin used typically depends on the absorption capacity, the oxygen head-space, the oxygen permeation rate and the desired shelf-life. The preferred thickness of the oxygen absorbing layer is between about 5 μm and about 100 μm, more preferred between about 10 μm and about 30 μm. In a preferred embodiment, the configurations involve using an ultraviolet photo-activated oxygen absorber is incorporated either beneath the laminate on the lid or as a co-

> extruded material as part of the blister. The photo-activated oxygen absorber is typically activated prior to sealing the drug into the blister package. *Other activation methods can also be employed. Suitable methods include electron beam, gamma irradiation and microwave treatment*. It will be appreciated by those skilled in the art that activation enables the processing (extrusion, molding or coating) and storage of the resin and package in air without oxygen scavenging prior to final packaging with the pharmaceutical. As such, any activation mechanism which effectively switches on the oxygen absorbing ability of the system at the appropriate time (generally immediately before or after the drug is sealed in the unit dose package) will be effective in the practice of the present invention.

Further, Claims 4 and 24 of Waterman specifically recite "oxygen absorber is selected from the group consisting of a moisture-activated absorber, a self-activated absorber, a UV-activated absorber, an electron beam activated absorber, a radiation activated absorber, a microwave activated absorber and combinations thereof." Thus, Applicants submit that Waterman, as a representation of the art, clearly establish that the artisan would appreciate the meaning of the oxygen absorbers set forth in the claimed invention and, as such, the written description requirement is satisfied.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejections of:

(a) Claims 2-3, 5-6, 8-12, 14-18, 22-23, 25-26, and 28-35 under 35 U.S.C. §103(a) over Hoogenboom (NL9400940) in view of Mills (US 5,686,104) as evidenced by Singh (US 2003/0175338) and Waterman (US 2002/0132359), Townsend (2002), and Shriver (1986),

(b) Claims 7 and 27 under 35 U.S.C. §103(a) over Hoogenboom in view of Mills as evidenced by Singh, Waterman, Townsend, and Shriver and further in view of Pilchik (Pharma. Tech. 2000),

(c) Claims 2-5, 6, 8-12, 14-18, 22, 23, 25, 26, and 28-35 under 35 U.S.C. §103(a) over Pflaum (WO 01/93859) as evidenced by Singh, Waterman, Townsend, and Shriver,

(d) Claim 7 and 27 under 35 U.S.C. §103(a) over Pflaum as evidenced by Singh, Waterman, Townsend, and Shriver and further in view of Pilchik;

are obviated by amendment.

Applicants make no statement with respect to the propriety of these grounds of rejection and in now way acquiesce to the same. Solely to expedite examination of this application, Claims 14 and 16 have been amended to include the limitations of Claims 4 and 24, respectively. Accordingly, these rejections are without merit and should be withdrawn. Applicants reserve the right to separate argue each of the dependent claims at a later date should it become necessary.

Withdrawal of these grounds of rejection is requested.

The rejections of:

(a) Claims 4 and 24 under 35 U.S.C. §103(a) over Hoogenboom in view of Mills as evidenced by Singh, Waterman, Townsend, and Shriver and further in view of Joshi (US 5,180,589), and

(b) Claims 2-5, 6, 8-12, 14-18, 22, 23, 25, 26, and 28-35 under 35 U.S.C. §103(a) over Pflaum as evidenced by Singh, Waterman, Townsend, and Shriver,

are respectfully traversed.

Pflaum is discussed at page 2, lines 16-23, as follows:

> WO 01/93859 solves the stabilization of HMG-CoA inhibitors, and among them also of atorvastatin, using a substance capable of binding and neutralizing carbon dioxide. Carbon dioxide is, according to the authors of the application, the most important factor leading to the instability of the product. Its effect is ascribed to the lowering of pH, which results in the decomposition of hydroxyacids particularly to their lactones. It is pointed out that gastric troubles may be caused if a medicine with a high content of alkaline substances is administered to patients. This fact limits the possibility of improving the stability by adding a stabilizer to the dosage form.

Pflaum is representative of the art prior to the present invention, including Mills which the Examiner relies upon as disclosing a composition containing atorvastatin. As stated at page 2, lines 30-32:

> Accordingly, it follows from the prior art that the main methods how to solve the problem of the stability of atorvastatin in a dosage form were either increase of the pH of the dosage form, or prevention of the lowering of the pH by CO_2 contained in the atmosphere.

That is, the presently claimed invention solves a problem previously existing in the art with respect to the stability of compositions comprising atorvastatin. These problems are discussed on page 3, lines 1-6:

> Despite these measures, the dosage forms of atorvastatin, and particularly if amorphous atorvastatin is in these forms, showed significant instability. Although the formation of undesirable products such as the lactone of atorvastatin was prevented, the formation of other unknown substances occurred. The active substance itself, not in the dosage form, showed even worse stability. Therefore, it was necessary to store and transport amorphous atorvastatin at about –20 °C. Naturally, these measures increased the costs of the said operations.

The Examiner suggests that Waterman disclose utilizing oxygen absorbers in order to help stabilize oxygen sensitive compounds. Applicants note that page 3, line 22 to page 4, line 6 discusses this possibility in relation to Waterman:

> In patent application US 2002/0132359, the use of these absorbers for pharmaceutical preparations sensitive to oxygen is applied for protection. The application is carried out in a blister packing where the absorber is situated between the lid and the blister itself. The application further informs that it is very difficult to find out which of the substances will be susceptible to oxidation. The problem subsists in the fact that often the oxidation does not follow the classical Arrhenius equation, and that is why accelerated stability tests, which are successfully used for other decomposition reactions, fail. The patent application further contains a list of some pharmaceutical substances, which could be sensitive to oxygen. HMG–CoA inhibitors simvastatin or lovastatin are the most relevant ones among them. Both these substances contain a system of conjugated double bonds in a carbocyclic system, which can result in sensitivity to oxygen.
>
> However, new facts have now surprisingly shown that degradation of atorvastatin, which does not contain this carbocyclic system is also caused by atmospheric oxygen. Moreover, it has been shown that the

> usual solution to the problem – the pharmaceutical composition containing a substance susceptible to oxidation –, that is the use of a formulation with an antioxidant, has, in the case of atorvastatin (stated, for example, in EP 680320), failed (example 6 of this document).

Certainly, Waterman shows that the artisan know the scope of oxygen absorbers, but degradation of atorvastatin still persisted.

The present inventors solved the problems heretofore existing in the art by providing a method for the stabilization of a pharmaceutical active solid substance atorvastatin embedded in a gaseous mixture by stabilizing a drug in the form of tablets or capsules containing atorvastatin in an amount of 1 to 60 % by weight of the total weight of the dosage form, packaged in a blister pack, and maintaining a partial pressure of oxygen of at most 2 kPa in the surrounding gaseous mixture wherein the said partial pressure of oxygen is achieved by packaging in a blister-forming machine, by introducing a stream of an inert gas into cavities in a lower shaped sheet with such intensity that the content of the gas in the cavity exchanges at least once, wherein the stream of the inert gas is introduced at a flow rate ranging from 180 to 3000 l/h (Claim 14) or wherein a band with shaped cavities is brought into a purging chamber, comprising a set of nozzles, destined for targeted introduction of the inert gas to the cavities, and of diversion channels for a washed-out air outlet, the purging chamber being located in a box having permanently inert atmosphere, wherein, subsequently, an upper covering band is pressed against said band with the cavities and, finally, the blister pack is welded together (Claim 16). Critical to the solution to the aforementioned problems is that atorvastatin is in a mixture containing solid magnesium oxide in an amount of 0.1 to 50 % by weight.

It remains that the Examiner has done nothing but use Applicants invention as a guidepost to bring together several disparate references each individually standing for an individual concept of the claimed invention, but each failing to provide the requisite disclosure necessary to bring their teachings together. The Examiner's alleged case of obviousness in view

of the cited art, is nothing more than "*a posteriori*" argumentation which is largely based on Applicants' invention rather than the state of the art existing at the time of their invention. The Examiner is reminded that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art" (MPEP 2142; see also MPEP 2145(X)(A)).

It remains that the critical notion of the stabilization of atorvastatin provided in the claimed methods is not disclosed, suggested, or even apparent based on the cited art. The Examiner offers no evidence that the problems sought to be solved in the secondary references that do not disclose atorvastatin is remotely similar to those recognized as needing to be solved in the disclosure of atorvastatin (see discussion above). Thus, the Examiner's position is that modifications in the cited references would have been within the general abilities of the skilled artisan, a statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). At best, the combined disclosures could be taken as an "invitation to experiment" or could be viewed as providing an "obvious to try" argument; however, "obvious to try" has long been held *not* to constitute obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007) does not eliminate the "obvious to try is not obvious" standard, as it clearly states that "obvious to try" may constitute obviousness, but only under certain circumstances. Specifically, *KSR* stated that

the fact that a claimed combination of elements was "obvious to try" might show that such combination was obvious under 35 U.S.C. § 103, since, if there is design need or market pressure to solve problem, and there are finite number of identified, predictable solutions, person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation. However, the Examiner offers nothing to show how these factors apply and whether there would be such an expectation or anticipated success.

Applicants respectfully submit that the Examiner has not offered any evidence that there is a recognized "design need or market pressure to solve the problem". Indeed, the cited art makes no suggestion that such a need even exists. Further, the Examiner fails to show that there are a "finite number of identified, predictable solutions". In fact, there is nearly an infinite number of ways that the ratio of branched amino acids may be modified. The Examiner also does not provide any evidence that a "person of ordinary skill in art has good reason to pursue known options within his or her technical grasp". It is clear from the cited art, in particular Mills and Pflaum, that the artisan had no such reason to modify the various disclosures to arrive at the claimed invention. All that the Examiner appears to provide is that arriving at the combination of components may be within the general abilities of the skilled artisan, but again this is not the proper standard for obviousness (*Ex parte Levengood*). Indeed, absent Applicants disclosure to serve as the guidepost, no objective reason to combine the teachings in a way that would place the artisan in possession of the claimed invention can be found.

The fact of the matter remains, there must be some reasonable expectation of success. To this end, "the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success." *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants submit that for the reasons discussed in the

background of the present invention, no reasonable expectation existed in the art prior to the presently claimed invention.

Applicants remind the Examiner that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness... Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" To this end, the Examiner is referred to the Examples of the present application which clearly show the benefits flowing from the claimed method (see, for example, Example 8).

More specifically, the Examiner is referred to Example 5 in the specification, which shows a comparison of a sample where atorvastatin is in a mixture containing solid magnesium oxide in an amount within the scope of the claims to a sample without magnesium oxide. A preliminary analysis found the partial pressure of oxygen after completion of the experiment and revealed that the pressure in the vial atmosphere dropped to 0.3 kPa. The HPLC analysis showed that in the absence of the magnesium oxide, the amount of impurities was nearly three times higher. Certainly nothing in the cited art would have suggested such an effect.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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